Modifying the Drug Elution Profile for Neointimal Control – Distance and Accuracy Improved Simultaneously With a New Driver? –

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The development of drug-eluting stents (DES) has dramatically changed the management of patients with coronary artery disease and will change the indications for coronary artery bypass grafting.¹ Moreover, it reconfirms the importance of optimal medical therapy, while recognizing the limits of local treatment, especially for decreasing mortality rates.²

Article p 2097

Historically, “breakthrough” technologies in the field of interventional cardiology have been developed at intervals of approximately 1 decade. Thus, balloon angioplasty was applied in the early 1980s, bare metal stents (BMS) in the early 1990s, and DES were introduced in the early 2000s. Next-generation stents currently being tested and beginning to demonstrate promising outcomes must also target the enhancement of safety profiles. These can be divided into 2 categories: (1) DES with bio-absorbable polymer (which becomes a BMS after drug elution)³ and (2) drug-eluting bio-absorbable “scaffolding” technology (the platform disappears after drug elution).⁴ Thus, anticipating further advances in developing such promising bio-absorbable polymer technologies, it is now timely to ponder what we have learned from the experience gathered so far with durable polymer-coated DES.

The 3 basic components of DES, which together are considered crucially important for determining performance, are the drug, the polymer, and the stent platform. Recalling the first-in-man trial of sirolimus-eluting stents, different drug-elution patterns were compared and it was decided to adopt the “slow release” type (Cypher, Cordis, Miami Lake, FL, USA).⁵ Owing to its clinical success, gradual-elution for up to several months became the “model” for subsequent products. Furthermore, sirolimus-derivatives (ie, everolimus, zotarolimus, and biolimus A-9, the so-called “limus family”) have been extensively used in DES, and have mostly achieved good results.

Control of neointimal hyperplasia (NIH) is a primary objective of using DES. Optimal neointimal control not only requires reducing the “average” NIH, but also minimization of its “variations” (ie, lesion-to-lesion variation and distribution along the length of the vessel). If such variations can be minimized, average NIH is theoretically no longer so impor-

tant, because of the accurate prediction of late lumen dimension at the time of the procedure. However, in practice, we have learned that there is a relationship between these variations and the average degree of NIH. To minimize such variations (to obtain the most consistent clinical outcomes), at the very least we need to equip current DES with a durable polymer that will give them a strong NIH suppressive capacity.

The zotarolimus-eluting stent, Endeavor (Medtronic, Santa Rosa, CA, USA), has shown unique performance. Its neointimal suppression capacity is relatively low compared with the other approved DES, thought to be related primarily to a shorter drug-elution period (mostly within 2 weeks) because of the nature of its biocompatible polymer. Accordingly, the polymer was modified to resolve this problem of a short drug-elution period, and the result was designated Endeavor “Resolute” (85% of the drug elutes within 60 days but elution continues up to 180 days). The difference between the original and modified versions resides solely in the polymer applied, whereas drug, drug dose, and the “Driver” stent platform are identical. Therefore, their comparison illustrates how differences in the polymer or drug-elution profile affect stent performance. The study by Waseda et al in this issue of the Journal confirmed the sustained stronger neointimal suppression by the Resolute stent during up to 9 months follow-up.⁶ An advantage of this study group is that the authors analyzed a series of DES trials conducted over a decade and pooled the data accumulated by consistent intravascular ultrasound methods.⁷ According to their study, in terms of neointimal control, Resolute is superior to the other zotarolimus-eluting stents, and almost equivalent to Cypher. Modification of drug-elution profiles is thus shown to alter efficacy.

Maximizing safety is the other objective of DES. Concerns regarding late or very late stent thrombosis (ST) remain as the biggest unresolved issues of DES use. NIH reduction and optimal coverage of stent struts seem to be essentially contradictory aspects of DES. However, we still do not precisely understand the relationship between the degree of NIH and the probability of ST. Some vascular “over-reactions”, such as late incomplete stent apposition (LISA), are considered likely to be associated with ST. Endeavor is slightly less effective in neointimal control, but guarantees low rates of LISA (0–1%).⁸ Given the enhanced efficacy, LISA occurred rather more frequently (6.7%) with Resolute, as first reported

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here by Waseda et al.⁶ At the moment, trade-offs between the strength of neointimal suppression and the probability of LISA vary between the different DES. To the best of our knowledge, everolimus-eluting stents (Xience, Abbott Vascular Inc, Santa Clara, CA, USA) have shown a well-balanced performance, with less late loss (0.1–0.2 mm) and the least LISA (0–1%). Potential factors contributing to such variability between DES presumably reside somewhere in stent design, polymer, drug, drug dose, elution profile, or elsewhere, but those factors remain unclear at present.

In the clinical setting, we have often encountered events contradictory to our expectations, and have noticed some gaps between the “ideal and reality” of DES use. The Endeavor stent uses a cell membrane-like coating, as well as accommodating relatively large amounts of neointimal coverage; thus, the consensus would be that the incidence of thrombotic complications should be low. In fact, the pivotal trials of Endeavor performed for clinical approval did show very low incidence of these events, remaining low over an extended follow-up period. However, at the same time, several independent randomized trials in real-world settings, including SORT-OUT III⁹ and ZEST, did provide data to the contrary (ie, increased probability of definite ST in Endeavor-vs-Cypher).

So, we must ask why such discrepant phenomena were observed? Potential overestimation may underlie the current definition of ST. Discrimination of cases of diffuse restenosis or new onset acute coronary syndrome in the target vessels is difficult. Furthermore, Cypher’s potential superiority might have been rather enhanced because of the relatively large vessels enrolled in both studies. However, considering the long-term advantage of using less inflammatory biocompatible polymer, the possibility of different outcomes at longer follow-up periods remains. In fact, in SORT-OUT III, the incidence of ST with Endeavor was still twice as high as Cypher at 18 months, but statistical significance had disappeared because of the slight increase of very late ST with Cypher.

According to accumulating evidence, including data from other DES trials, mild to moderate angiographic late loss when using durable polymer DES may not directly correspond to improved safety. Increased NIH implies improved strut coverage, but at the same time, raises the chance of lumen stenosis that potentially enhances local thrombogenicity caused by blood flow velocity reduction and turbulence. Despite clearly insufficient data, it is doubtful whether the increased incidence of LISA using Resolute is truly more problematic than the increased risk of lumen narrowing with Endeavor in terms of the probability of ST.

To achieve a good balance between efficacy and safety

appears to be a major challenge in the development of DES, perhaps similar to the relationship in golf between “distance and accuracy” when driving off (ie, difficult to achieve both simultaneously for common players). However, we notice that a truly strong player does frequently hit long and consistent tee shots by mostly keeping to the fairway. Probably, the same things happen to DES. To sum up, “efficacy and safety really go hand in hand”, don’t they? I wonder if such compatibility may actually be the unexpected reality hidden in the accumulated data of the approved DES. It can be reasonably expected that this new driver will ameliorate both problems together.

Disclosures

Dr Morino was a consultant for Medtronic, received honoraria for lectures from Johnson & Johnson, and is a member of the advisory board for Abbott Vascular.

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